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10/088,567	03/19/2002	Shizuo Akira	31671-178057	3078

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 10/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

NC

Office Action Summary	Application No.	Applicant(s)	
	10/088,567	AKIRA ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *1-16,21-30 and 32-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-20 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/19/02;7/22/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner prosecuting this application has been changed. Any inquiries relating to the examination of the application should be directed to Examiner Singh. The telephone number is provided at the end of this office action.

Election/Restrictions

Applicants' election of claims 17-20 and 31 (Group IV) in the reply filed on July 18, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-16, 21-30 and 32-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 18, 2006.

Claims 17-20 and 31 are under current examination.

Priority

Applicant has been denied foreign priority because a certified English translation of the PCT/JP 01/04731 and foreign application, JP 2000-219652, has not been filed.

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a translation of the foreign application should be submitted under 37 CFR 1.55 in reply to this action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-20 and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse comprising in its genome a mutated TLR-9 allele such that no functional N-terminal fragment of TLR 9 is produced and wherein peripheral macrophage of said mouse exhibit decreased responsiveness to CpG ODN (bacterial DNA), does not reasonably provide enablement for any other animal comprising any other gene encoding a receptors from any other organisms that specifically recognize bacterial unmethylated CpG sequences that is expressed or deleted or any other nonhuman animal as broadly embraced by these claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working example are not disclosed in the specification, therefore enablement issues are raised and discussed based on the state of knowledge

pertinent to an art at the time of the invention, therefore, skepticism raised in enablement rejections are those raised in the art by artisan of expertise.

Claims 17-20 and 31are broad in scope. The following paragraph will outline the full scope of the claims. These claims are broad in scope, encompassing any nonhuman mammal subsequently limiting to mouse. In addition, instant claims embrace any nonhuman animal comprising any gene encoding a receptor protein specifically recognizing bacterial DNA having an unmethylated CpG sequence that is either expressed or destroyed. The disclosure provided by the applicant, in view of prior art, must encompass a wide area of knowledge to a reasonably comprehensive extent. In other word each of those, aspect considered broad must be shown to a reasonable extent so that one of the ordinary skills in the art at the time of invention by applicant would be able to practice the invention without any undue burden being on such Artisan.

The claims are directed to a transgenic nonhuman animal comprising a gene encoding a receptor protein specifically recognizing bacterial DNA having an unmethylated CpG sequence and a transgenic knockout nonhuman animal wherein receptor protein specifically recognizing bacterial DNA having an unmethylated CpG sequence is mutated or deleted such that nonhuman animal does not show any reactivity against bacterial DNA.

The invention features methods of making non-human animal excessively expressing a gene encoding a receptor protein specifically recognizing bacterial DNA having the unmethylated CpG sequence such that said non-human animal producing a large amount of receptor proteins specifically recognizing bacterial DNA having an unmethylated CpG sequence compared with wild-type non-human animals (see page 11, last paragraph of the specification). It is also noted that claim 18 embraces non-human animal whose gene function encoding a receptor protein specifically recognizing bacterial DNA having an unmethylated CpG sequence is deleted or inactivated by genetic mutations such as damaged, deleted, substituted (see page 12, first paragraph). The specification exemplified a knockout mouse of TLR9 that is, a knockout mouse lacking receptor proteins specifically recognizing bacterial DNA having an unmethylated CpG sequence. It is noted that specification discloses that TLR9 gene is substituted

with pMC1 neo gene cassette, and a targeting vector is introduced into ES cells by homologous recombination (see page 13, paragraph 2 and 3) which is then introduced in mouse blastocysts that is implanted into pseudo pregnant mouse to obtain a chimeric mouse (see page 13). The specification while provides guidance for a method to make transgenic knockout mouse using ES cell but does not provide any guidance how to make any other knockout or transgenic nonhuman animal comprising any other gene encoding a receptor protein specifically recognizing bacterial DNA.

As a first issue, the claims 18-19 and 31 embrace the creation of transgenic nonhuman animal that includes any species subsequently limiting to mouse. The specification has contemplated introducing a targeting constructs in mouse embryonic stem cell by homologous recombination, and microinjecting said mouse embryonic stem cell into mouse blastocysts; and implanting the blastocysts comprising the mouse embryonic stem cell into pseudo pregnant mouse and then allowing the resulting pregnant mouse to deliver viable chimeric offspring and then producing a transgenic TLR9 knock out mouse. The exemplified TLR9 knockout mouse uses mouse ES cell. The art at the time of filing further held that transgenic technology was not predictable for any species other than mouse. Since the specification discloses using mouse ES cells to produce knockout mice via homologous recombination of targeting vectors in the ES cells, ES cells from various species are required to produce various heterozygous or homozygous TLR9 knockout non-human animals. Houdebine et al (Journal of Biotechnology, 1994, Vol., 34, pp 269-287) describe that although ES cells can be used to generate transgenic animals, but this approach remains restricted to mice, ES cells from other species are not presently available (pp 279). In addition, Mullin et al also point that non-mouse ES cell capable of providing germ line chimeras were not available (Mullins et al., Journal of Clinical Investigation, 1996, pp 1557, 1st paragraph). Campbell and Wilmut (1997, Therigenology) acknowledges report of ES-like cells in number of species, but also emphasize that there are no report of any cell line that contribute to germ line in any species other than mouse (pp 65; 2nd paragraph). Thus, the state of the art is such that ES cell technology is generally limited to the mouse system and that only putative ES cells exist for other species (Moreadith et al., J.

Mol. Med., 1997 p214, abstract). Even at the time of filing of instant application, Hochepied et al (Stem Cells, 2004, 22, 441-447; abstract) state "transmission of the genotype to the offspring of chimers have only been achieve with mouse ES cells". Note that "putative" cells lack a demonstration of the cells to give rise to germ line tissue or the whole animal, a demonstration that is an art recognized property of ES cells. Therefore, at the time of filing of this application, non human transgenic animals could not be prepared for any species other than mouse with disclosed phenotypes. The specification does not teach how to make any knockout nonhuman animal for any other species other than mice or correlate making mice to making knockout for any other species. Therefore, the claims should be limited to mouse and method for gene knockdown in mouse as discussed in the office action.

As a second issue claim 18 as recited do not require any phenotype subsequently limiting to a phenotype that is characterized by no reactivity against bacterial DNA. It is noted that the specification dose not provides adequate correlation between phenotype obtained in the mice to the phenotype obtained in other species. The state of the art at the time of filing uses that the phenotypes of transgenic mice does not predict the phenotype in non-mice species. Models of human diseases have relied on transgenic rats when the development of transgenic mice having the desired phenotype was not feasible. Mullins (Nature, 1990, 344; 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse Ren-2 renin trasngene. Hammer et al (Cell, 1990, 63: 1099-1112) describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both the investigators were preceded by the failure to develop human disease like symptoms in transgenic mice (Mullins, 1989, EMBO, 8: 4065-4072; Taurog, 1988, J. Immunology, 141: 4020-4023) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats. Therefore, the specification dose not enable making transgenic having the disclosed phenotypes in species other than mice.

As a third issue, claims 18-19 and 31 embrace a nonhuman animal wherein gene encoding a receptor protein is destroyed on a chromosome. Since destroyed has

variable interpretation and even Applicants specification contemplated sequence is deleted or inactivated by genetic mutations such as damaged, deleted, substituted (see page 12). The specification describes a targeting vector that is constructed by replacing a 1.0 kb fragment encoding part of LRR (leucine-rich repeat) region with a neomycin-resistance gene cassette (see example 2). At the time of filing of this application, Holschneider et al. (Int J Devl Neuroscience, 2000, 18: 615-618) state that single genes are often essential in a number of different physiological processes. Hence deletion of an individual gene may prove so drastic or so widespread as to create an amalgam of phenotypes whose interpretation becomes confounded by the interaction of various new physiologic changes (pp 615). Holschneider et al discuss various factors that contribute to the resulting phenotype of transgenic mice, including compensatory system that may be activated to mask the resulting phenotype; these compensatory changes may be due to differential expression of another gene, which may be regulated by the downstream product of the deleted gene. Thus, at the time of filing, the resulting phenotype of a knockout mouse was considered unpredictable and it was confounded by multiple compensatory pathways. The specification does not teach a transgenic mouse comprising any disruption would result in expected phenotype. In absence of any specific teaching an artisan of skill would have to perform undue experimentation to make and use the invention.

As a fourth issue, claims 17 and19 are directed to a nonhuman animal wherein gene encoding a receptor protein is excessively expressed. The specification describes a non-human animal excessively expressing a gene encoding a receptor protein specifically recognizing bacterial DNA having the unmethylated CpG sequence of the present invention can be any non-human animal producing a large amount of receptor proteins specifically recognizing bacterial DNA having an unmethylated CpG sequence compared with wild-type non-human animals (see page 11, last pargarph). It is noted that as recited claims 17and 19 read on transgenic nonhuman animal over expressing gene-encoding protein that recognizes bacterial DNA or any nonhuman animal whose host cell express such gene. The specification does not provide any specific guidance as to how gene-encoding protein that recognizes bacterial DNA will be expressed at

high level. Although great advances have occurred in transgenic technology, the state of the art of generating transgenic animals is such that the resulting phenotype would not be predictable. This is because the art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have within their cells cellular mechanisms which prevent expression of the transgene, such that DNA methylation or deletion from the genome (Kappell et al Current Opinions in Biotechnology 3, p. 549, col 2, par 2, 1992). Mullins et al states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into different species of animal has been reported to give divergent phenotypes (Mullins et al Hypertension 22:631, col 1, par 1, lines 14-17, 1993). The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without general rules to obtain good expression (e.g. specific promoters, presence or absence of introns, etc. (Houdebine J. Biotech 34:281, 1994). "The position effect" and unidentified control elements also are recognized to cause aberrant expression (Wall. Theriogenology 45:61, par 2, line 9 to p. 62, line 3, 1996.) Mullins et al disclose that "the use of non-murine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to the another." (Mullins et al. J Clin Invest 98:S39 summary, 1996) Well-regulated transgene expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron Mol Biotech 7:256, col 1-2, bridging par, 1997). Factors influencing low expression, or lack their of, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron et al Mol Biotech 7:256, lines 3-9). These factors, thus, are copy number independent and integration site dependent, emphasizing the role the integration site plays on expression of the transgene (Cameron Mol Biotech 7:256, lines 10-13). Furthermore, Sigmund states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and

that the position of the transgene effects expression, and thus the observed phenotype (Sigmund et al Arteroscler Throm Vasc Biol 20:1426, col 1, par 1, lines 1-7, 2000). With regard to the importance of promoter selection, Niemann states that transgenic pigs made with different promoters regulating expression of growth hormone gene give disparate phenotypes, one deleterious to the pig, the compatible with pig health (Neimann Trans Res 7:73, col 2, par 2, line 12 to p. 73, col 1, line 4, 1998). While the intent is not to say transgenic animals of a particular phenotype can never be made, the intent is to provide art taught reasoning as to why the instant claims are not enabled. Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for any transgenic non-human animal, it would have required undue experimentation to the levels of the transgene product, the consequences of that product, and therefore, the resulting phenotype. The specification fails to provide teachings or specific guidance to overcome the above-described unpredictabilities, in order to successfully produce a nonhuman animal with a specific phenotype, and as such, the claims are not enabled.

In view of the lack of teachings or guidance provided by the specification with regard to an enabled nonhuman transgenic animal comprising a gene encoding that recognizes a bacterial DNA that is either expressed or destroyed, the lack of teaching or guidance provided by the specifications to overcome the art recognized unpredictability of expression pattern, resulting phenotype and for the specific reasons cited above it would have required undue experimentation for an artisan of skill to make and use the claimed invention. It would require undue experimentation for an Artisan to make and use the claimed invention and/or working examples demonstrating the same, such invention as claimed by the applicant is not enabled for the claimed inventions commensurate with the full scope of the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-20 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim embraces a gene encoding a receptor protein specifically recognizing bacterial DNA having unmethylated CpG sequence.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1 117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

As recited claims embrace any gene sequences encoding receptor protein specifically recognizing bacterial DNA having an unmethylated CpG sequence from all species. Based upon the prior art there is expected to be sequence variation among the species of DNA sequences of gene from different species. The specification has provided the description of mice TLR-9 sequence showing contemplated biological activity. The specification however has not disclosed the sequences of any of the other gene embraced by the claims. There is no evidence on the record of a relationship between the structures of the DNA molecules of any of the embraced gene encoding a receptor protein such as TLR9 that would provide any reliable information about the structure of DNA molecules within the genus. There is no evidence on the record that embraced gene encoding a receptor protein specifically recognizing bacterial DNA had known structural relationships to each other; the art indicated that there is variation between DNA sequences of various gene sequences. The claimed invention as a whole

is not adequately described if the claims require essential or critical elements or motifs which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Additionally, to the extent that the claims are intended to encompass DNA encoding receptor protein specifically recognizing bacterial DNA by hybridizing mouse derived DNA library with part or whole of a sequence of bases shown in SEQ ID NO: 1 or its complimentary sequence under stringent condition (see specification page 7 last paragraph and page 8, first paragraph). Thus, it is apparent that hybridization is also contemplated in the specification, however the specification does not provide any functional properties to the resulting sequence. There is no evidence on the record of a relationship between the structures of the DNA molecules of any of the sequence that would provide any reliable information about the structure of DNA molecules within the genus. In addition, specification fails to provide any guidance to how modification to one species disclosed can be made while maintaining the required biological activity. For example, a sequence of 20 to100 base pairs from the SEQ ID NO 1 as disclosed in the specification will hybridize, however if it does not contain the essential motifs that are required for contemplated biological activity, such a sequence will hybridize to SEQ ID NO: 1 but will not be functional and show contemplated biological activity. The specification does not provide any disclosure as to what would have been the required structure for a complimentary sequence or small fragments, or sequence that will hybridize and whether the structure is present in various species of mammals or how does it vary. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics. Inc.*, 48 USPQ2d 1641, 1646 (1998). In the instant case, the claimed embodiments of gene encoding a receptor protein specifically recognizing bacterial DNA sequence, other than the mice TLR9 sequence encompassed within the genus of such gene sequences lack a written description. The specification fails to describe what DNA molecules fall into this genus. The skilled artisan cannot envision the detailed chemical structure of the encompassed gene

sequences showing contemplated biological activity, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).
One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 UsPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of the above considerations, one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by member of the genus of gene sequences encoding a receptor protein that specifically recognizes bacterial DNA, other than the mouse TLR9 sequence. Moreover, the art has recognized that there would be variation among the species of the genus of DNA sequences of such gene sequences.

Therefore, Applicant was not in possession of the genus of gene sequences encoding a receptor protein that specifically recognizes bacterial DNA as encompassed by the claims. *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-20 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 18 recite, "wherein the function of the gene...is destroyed on a chromosome". It is generally known in the art that nucleic acids comprised within genes of chromosomes are deleted when carrying out standard genetic recombination techniques, however, it is unclear how a function of a gene is deleted nor is it clear what is meant by said recitation. Claims 19 and 31 depend on claims 19.

Claims 18-19 and 31 are indefinite since meets and bound of term "destroyed" is unclear. In the instant case, claims embrace a nonhuman animal having a gene sequence that is destroyed on the chromosome. It is unclear whether gene is destroyed because of chemical reaction or gene targeting or any other reason. Since the term "destroyed" could have variable interpretation depending on Artisan, meets and bound of term is unclear.

Claims 20 and 31 recite the limitation "rodent animal" in claims 17 and 18. There is insufficient antecedent basis for this limitation in the claim since neither claim is specifically drawn to rodent animals.

Claims 17 recite a term "excessively" which is a relative term which renders the claim indefinite. The term " excessively " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In the instant case, it is unclear gene encoding protein of the invention is excessively expressed as compared to which protein or nonhuman animal. Claim 20 depends on claim 17. Appropriate correction is required.

Claims 19-20 and 31 recite a limitation "according to" that simply requires to bring into agreement. Since, according only implies a level of agreement between two, thus meets and bound of instant claims 19-20 and 31 are unclear and this limitation does not further limit the instant claim. It is emphasized that more specific reference to animal will obviate this rejection. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 17-20 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Bauer et al (US Patent No 6,943,240, dated 9/13/2005; effective filing date 9/15/2000).

It is noted that the instant rejection is put forth because the Bauer reference has a 102(e) date availability due to the foreign priority document not having been perfected. A certified English translation of the foreign priority document would remove the availability of the Bauer reference under 102(e) if all the claimed subject matter is in fact disclosed in the foreign priority document.

The claims are directed to a non-human animal, more specifically, a mouse, wherein a gene encoding a receptor that specifically recognizes bacterial DNA having an unmethylated CpG sequence is excessively expressed.

Bauer et al disclosed a method to make transgenic nonhuman animal including mouse comprising in its genome a nucleic acid encoding TLR9. Bauer et al also disclose constitutive expression of TLR9 in the transgenic animals (see column 40, lines 45-52). In addition, Bauer et al also taught inactivation or replacement of the endogenous TLR9 gene could be achieved by a homologous recombination system using embryonic stem cells. Buaer contemplate that resultant transgenic non-human

mammals having a TLR9-/- knockout phenotype may be made transgenic for the murine TLR9 and used as a model for screening compounds as modulators (see column 40, line 66 bridging to column 41, lines 1-5).

Accordingly Bauer et al anticipate claims 17-20 and 31.

Claims 18-19 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Takeuchi et al (Immunity, Oct. 1999, 11, 443-452).

Takeuchi et al disclosed taught a transgenic knockout mouse, wherein a gene encoding a receptor protein (TLR2) that recognizes bacterial DNA is deleted. Takeuchi et al disclosed a mouse TLR2 and TLR4 gene is disrupted by introducing a targeted mutation in to ES cells. The results show that TLR 2 deficient macrophage lacked the response to gram-positive bacterial cell wall while TLR4 deficient macrophage lacked response to gram-positive lipoteichoic acid (see abstract).

Accordingly Takeuchi et al anticipate claims 18-19 and 31.

Claims 18-19 and 31 are rejected under 35 U.S.C. 102(a) as being anticipated by Hemmi et al (Nature. 2000 Dec 7; 408(6813): 740-5).

It is noted that the instant rejection is put forth because the Hemmi reference has 102(a) date availability due to the foreign priority document not having been perfected. A certified English translation of the foreign priority document would remove the availability of the Hemmi reference under 102(a) if all the claimed subject matter were in fact disclosed in the foreign priority document.

Hemmi et al teach a TLR9-deficient ($TLR9^{-/-}$) mice that does not show any response to CpG DNA, including proliferation of splenocytes, inflammatory cytokine production from macrophages and maturation of dendritic cells. It is noted that $TLR9^{-/-}$ mice dislcosed by Hemmi showed resistance to the lethal effect of CpG DNA without

any elevation of serum pro-inflammatory cytokine levels (see abstract and page 743, Gigure 3).

Accordingly Hemmi et al anticipate claims 18-19 and 31.

Double Patenting

Claims 18-19 and 31 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 10/517,663 (US Patent Publication no 2006/0059579). Even though the conflicting claims are not the same, they are not patentably distinct from each other because both sets of claims encompass a method of treating or preventing HIV infection by transplanting stem cells having a beneficial gene.

For example, claim 18 of instant application broadly encompasses a nonhuman animal wherein gene encoding a receptor protein specifically recognizing the bacterial DNA is destroyed on the chromosome. Claim 19 limit the nonhuman animal of claim 18 to include a phenotype showing no reactivity against bacterial DNA. Claim 31 limits the nonhuman mammal of claim 18 to include a mouse. Whereas, Claim 1 of the application No. 10/517,663 is directed to a nonhuman animal model non-responsive to mycobacterial lipoproteins/lipopeptides, wherein the function of the gene encoding a protein specifically recognizing mycobacterial lipoproteins/lipo peptides is deleted on its chromosome. Claims 2-7 recite a mouse that is a TLR1 knockout mouse generated by constructing a targeting vector by substituting a whole or a part of the gene fragment of the gene site including the intracellular and trans membrane domain of the TLR1 gene. Thus, the claims of instant application differ only with respect to broader scope of gene encoding a receptor protein that recognizes bacterial DNA, which is encompassed by the transgenic mouse disclosed in '663 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Conclusion

No Claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272- 0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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